PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 January 2000 (07.01.00)	
International application No. PCT/US99/11969	**Applicant's or agent's file reference** X-12279
International filing date (day/month/year) 01 June 1999 (01.06.99)	**Priority date** (day/month/year) 01 June 1998 (01.06.98)
Applicant HUANG, Lihua et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 December 1999 (02.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Kiwa Mpay

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11969

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12N 9/64, 15/OO, 15/57, 15/70, 15/79

US CL :435/226, 69.6, 252.3, 320.1; 514/8; 536/23.2, 23.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/226, 69.6, 252.3, 320.1; 514/8; 536/23.2, 23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN/Chemical Abstracts, DIALOG: Medline, Biosis Previews, Current BioTech Abstracts, Derwent Biotechnology Abstracts

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	KATSUMI. A. et al. The Carboxyl-Terminal Region of Protein C is essential for Its Secretion. Blood. 15 May 1998. Vol. 91. No. 10. pages 3784-3791, especially pages 3785-3790 and Figures 1 and 5.	1, 3, 5, 7, and 8 2, 4 and 6
Y	EHRLICH. H.J. et al. Direct Expression of Recombinant Activated Protein C, a Serine Protease. The Journal of Biological Chemistry. 25 August 1989. Vol. 264. No. 24. pages 14296-14304, especially pages 14299-14303.	2, 4 and 6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

22 SEPTEMBER 1999

Date of mailing of the international search report

18 OCT 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

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Authorized officer

Ponnathapura Achutamurthy

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Form PCT/ISA/210 (second sheet)(July 1992)*

PATENT COOPERATION TREATY

PCT

31 JUL 2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-12279		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/11969	01 JUNE 1999	01 JUNE 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ELI LILLY AND COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02 DECEMBER 1999	26 MAY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PONNATHARURA ACHUTAMURTHY Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/11969

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-17, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 18, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [X] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/11969

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2, 4 and 6	YES
	Claims	1, 3, 5, 7 and 8	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-8	NO
Industrial Applicability (IA)	Claims	1-8	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Applicants' Response filed 21 April 2000 to the Written Report mailed 23 February 2000 indicates that they intend to defer any argument or amendment addressing statements of the Written Report until such time as National stage examination commences for applications stemming from this PCT application. Accordingly, the statements of the Written Opinion are restated in this International Preliminary Examination Report.

Claims 1, 3, 5, 7 and 8 lack novelty under PCT Article 33(2) as being anticipated by Katsumi et al., of record, who disclose, see Table 1 and Figure 1 at page 3785, recombinant preparation of an isolated human protein C polypeptide which comprises a light chain and a truncated heavy chain, lacking as many as 60 amino acids of the native heavy chain carboxyl-terminus. Katsumi et al. also disclose, see Table 2 at page 3787, that several forms of the expressed human protein C having a truncation of the heavy chain are activated and further disclose, see the **Materials and Methods** spanning pages 3784 and 3785, preparation of recombinant DNAs encoding the human protein C polypeptides having truncations of the heavy chain, an expression vector, pED, comprising the recombinant DNAs, and a mammalian host cell transformed with the expression vector. Thus the disclosure of Katsumi et al. meet all of the limitations of claims 1, 3, 5, 7 and 8.

Claims 2, 4 and 6 lack an inventive step under PCT Article 33(3) as being obvious over Katsumi et al. in view of Ehrlich et al., of record. The disclosures of Katsumi et al., discussed above, are taken as before and the disclosure of Katsumi et al. of a particular human protein C polypeptides heavy chain truncation, PC416, see Figure 1A, Figure 2B and Table 2, is now emphasized. Because Katsumi et al. used a cDNA transcribed from a different allele, the teaching of Ehrlich et al. of a specific nucleotide sequence of the cDNA of SEQ ID NO:2 herein is now cited. It would have been obvious to one of ordinary skill in the art to replace the cDNA of Katsumi et al. with the cDNA of Ehrlich et al. in preparing a PC415 human protein C polypeptide heavy chain truncation. just one amino acid shorter than the PC416 human protein C polypeptide heavy chain truncation, meeting (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 9/64, 15/00, 15/57, 15/70, 15/79; A61K 38/48 and US Cl.: 435/226, 69.6, 252.3, 320.1; 514 //8; 536/23.2, 23.5

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
limitations of claims 2 and 4. This is because such an artisan would have been well aware that the two cDNAs are interchangeable in their coding capacity up to that point and also because such an artisan would have had a reasonable expectation that a PC415 truncation variant would function just as well as the PC416 truncation variant of Katsumi et al. where Table 2 of Katsumi et al. shows that slightly shorter truncations have better activity than the PC416 truncation variant. Claim 6 depends from claim 1, and is considered obvious because Katsumi et al. show in Table 2 that the entire range of heavy chain truncation variants about the PC416 position have activity, thus such an artisan at that time would have had a reasonable expectation that such heavy chain truncation variants would be efficacious when administered to a patient in a method of treating thrombotic disorders, vascular occlusive disorders and hypercoagulable states.

Claims 1-8 the criteria set out in PCT Article 33(4), because the subject matter described by the claims is both useful and practicable without any undue experimentation.

---------- NEW CITATIONS ----------
NONE